BLOOD GAS CHANGES DUE TO SUBNORMAL BODY TEMPERATURES

By

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BOSTON UNIVERSITY

GRADUATE SCHOOL

Thesis

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B. S. Franklin and Marshall College, 1948

Submitted in partial fulfilment of the
requirements for the degree of
Master of Arts
1949

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I should like to express my sincere appreciation to Dr. Kenneth E. Penrod and the members of the Physiology Department for the guidance given me in planning and executing my research problems. I particularly wish to thank Miss Jean Flynn for her technical assistance without which much of the experimental work for this thesis could not have been completed.

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LITERARY REVIEW

Poikilotherms, animals lower in the phylogenetic tree than birds, adapt their body temperatures to that of the environment. In lower temperature their metabolism, circulation and general activity is decreased thus keeping their physiologic functions in equilibrium. During winter months these animals can thus live in a lowered state of activity without the necessity of food.

Slightly more advanced than the poikilotherms, are those mammals such as the bears, marmots, and opossums, which are homeothermic for the major portion of the year but hibernate during the winter. These animals have a decreased metabolism accompanied by a decrease in circulation and respiration during the cold months (8, 20).

It has been a matter of speculation how the hypothermic state of non-hibernating mammals resembled the hibernating state. A "pseudo-hibernating" state in rabbits has been described (2) in which the rabbits after having been lowered to a rectal temperature of 20° C. and then warmed to 23 to 28° C. showed no response to external stimuli but snored loudly, had a slow irregular pulse and recovered readily.

It has been found that rats younger than 10 days appear to be cold-blooded and can withstand subjection to cold (3° C.) for periods of 108 minutes, which older rats cannot tolerate (21). The younger rats, exhibiting no measurable metabolism under these conditions, would lead one to believe that this adaptation is another example of the recapitulation theory.

Warm-blooded animals confronted with a change in environmental temperatures have various mechanisms for temperature regulation of which vasoconstriction is probably the most important. By this action, the peripheral tissue will act as a "suit of clothes" (3). The shift of fluid from the blood stream to the skin, subcutaneous tissue and muscles (27) aids in the prevention of heat loss by reducing the peripheral flow, increasing the thickness of the tissue and thereby reducing the amount of heat lost by convection (4, 6). It has been shown by Perkins et al. (43) that vasoconstriction can also be found in sympathectomized animals.

The increase of metabolism (34) is the major mechanism for combating hypothermic conditions. Shivering in humans subjected to cold water (20, 25, and 30° C.) will start at a rectal temperature of 35 or 36° and will prevent a further decrease in temperature (54). Humans subjected to air temperature of 31° C. (29) will start to shiver, raising their rectal temperature 0.3 to 0.8° C. This act is accompanied by a vasoconstriction and may be due to a peripheral stimulation causing an epinephrine release. Upon injection of insulin shivering can be abolished (23). The increase in metabolism due to shivering is reported to be 180% and 400% of the normal (25, 51). Although heat production has been found to be proportional to shivering, it need not necessarily be associated with visible muscular contraction but may be associated with increased muscular tension alone. The stimulation of shivering varies with the individual animals. In some cases no drop in rectal temperature is necessary and in others shivering is not initiated until the rectal temperature drops 6° C. (51). The temperature range of the onset of shivering in anesthetized dogs (amytal, pentothal sodium) has been found to vary

with the depth of anesthesia by some investigators (23, 41) and is maintained until 30-22° C. At the termination of shivering, the metabolism decreases rapidly along with the respiration and pulse rate in animals as reported by many investigators (7, 25, 26, 35, 41, 45).

This reduction in metabolism has been utilized as a possible therapeutic use of hypothermia. Local application of temperatures in the 40° - 50° F. (4.4 - 10° C.) range to neoplastic lesions in humans can reduce both the pain and size of tumors (47). The cold has been shown to effect the tumor cells but not the normal cells. In this manner general lowering of body temperature has been used as a treatment for primary and metastatic cancer (52).

Hypothermia is sometimes used as a local anesthetic in private practice (ethyl chloride). Clinically cold has been used to relieve pain, fever, decrease inflammation, treat morphine addiction, leukemia, and schizophrenia (3, 52).

Throughout the literature on hypothermia there have been observations regarding circulation, metabolism and respiration. Attempts have been made to single out one of the three as the prime cause of death. It is, however, a difficult task to consider any one of the three related fields without the others, thereby making it very unlikely that the cause of death could be ascribed to any one factor.

During exposure to increased cold, hemoglobin absorbs and holds oxygen more avidly (17, 1). It is claimed by Rein (1) that this oxygen is not released resulting in local suffocation of the tissues. Many authors, therefore, consider hypoxic hypoxia due to lack of oxygen release from the blood as the prime factor above others causing ultimate death (1,

53, 54). One of the aims of this thesis is to produce evidence that would refute this theory.

The first circulatory changes observed in all animals subjected to a very cold environment are the increased heart rate, elevated blood pressure, and pronounced vasoconstriction. These changes are mentioned in almost all literature dealing with the topic. After the initial rise, the heart rate begins to decrease, showing a linear regression with temperature (2, 3, 6, 21, 32, 52). This gradual fall in heart rate is accompanied by a migration of the body fluids from the vascular channels to the interstitial spaces causing an apparent increase in the number of blood cells and a concentration of the blood plasma (3, 6, 9, 22, 27, 30, 44, 50, 52). The increase in blood concentration could be due to a mobilization of blood cells, or to the egress of fluid. Barbour and Hamilton (4) point out that the change must be due to the latter since the rapid nature of the response would not permit the production of new cells; likewise sympathectomy produces no change in the response. Mild edema of the extremities has been observed by Talbot (52) to occur in individuals exposed to cold. By analyzing edematous subcutaneous tissue procured by freezing portions of a dog's body, Harkins and Hudson (30) have found that the fluid was tinged with blood and would readily clot. It was found that the sugar was much less, the non-protein nitrogen and protein concentration were slightly less and the sodium chloride concentration was greater than that of the plasma. This evidence would lead one to believe that the fluid shift was due to increased capillary permeability. However, the permeability of the capillaries at decreased temperatures (9° - 15° C. for 10 min.), as determined by fluorescein injections, was

found by Lange to be decreased (37). Furthermore, Lange (37) and Spealman (48) found that the capillaries are dilated and the blood flow increased to low temperatures.

This increased concentration of blood acts to raise its specific gravity (54). The blood viscosity rises at a rate of approximately 2% for every 1° C. drop in temperature (19). In humans the viscosity was found to rise at 35° C. rectal temperature and continued to rise as the temperature fell (1).

Due to the vasoconstriction, viscosity rise and water shifts, the circulation time in humans is prolonged approximately 5% per degree F. fall in temperature as was shown by Oppenheimer and others (30, 40).

After the initial rise the pulse rate decreases faster than the blood pressure. At this time the pulse pressure and stroke volume increase (39). But, since a pronounced vasoconstriction and slowed circulation time obtains, Kossman (35) and Rodbard(45) conclude there is a diminished minute output of the heart.

It was found by Hamilton et al. (28) that the heart rate in non-anesthetized rats and kittens dropped linearly to 18.3° C. before it became irregular. Electrocardiographic studies revealed a lengthened P-R interval with an increased amplitude and width of the R and T waves.

These changes, leading to the overworking of the circulatory system and ultimate circulatory insufficiency in rats, have been summarized by Crismon (13) as follows:

1. Phase of compensating circulatory adjustments from 38 to 28° C.
    a. peripheral vasoconstriction
    b. slowed heart rate with increased stroke volume

2. Phase of progressive circulatory failure from 29 to 20° C.
    a. arterial pressure declining with slowing heart rate
    b. reduced cardiac output through reduced stroke volume

3. Phase of regional asphyxia below 19° C.
    a. signs of cardiac asphyxia
        (1) Impaired ventricular contraction
        (2) Atrioventricular block
    b. signs of asphyxia of the CNS
        (1) Respiratory failure

A common occurrence in terminal hypothermia is a distended heart, particularly the right heart (1, 54).

Metabolism is directly related to the circulation since circulation is necessary to remove the metabolites and transport the oxygen to the tissues. Eventually, metabolism is reduced in accord with Vant Hoff's law. It has been speculated by Murlin and Greer (39) that the decrease in metabolism closely follows the total heart action. Initially, on exposure to cold (25) the basal metabolic rate of humans was found to be 180% above normal. Twenty-four hours later, at a rectal temperature of 29.5° C., there was a drop in basal metabolic rate with further decreases at 48 and 72 hours. The initial metabolic response to cold is one of an increase, closely related to shivering, as determined by Penrod (41) in his oxygen consumption studies on dogs.

Shivering will cause an increase in metabolism of 170% above normal in 15 day old rats placed in a 20° bath (21). The effective heat production of shivering is illustrated by the fact that animals lightly narcotized are more difficult to cool than those in deep narcosis (27). The metabolism decreases when the shivering stops (41) and at this point the

animal will cool more rapidly. Barbour and Prince believe that the decreased metabolism is a contributing cause rather than the effect of a change in body temperature (5). It has also been found that the onset of shivering can be delayed by breathing a high oxygen concentration (36).

Coincident with shivering the respiratory quotient increases (33) and when shivering stops it decreases indicating that shivering may be associated with the metabolism of carbohydrates. After the cessation of shivering, even if the dogs be given glucose, the respiratory quotient will drop indicating that cooling the animals will change the nature of the metabolism involved to converting fats to carbohydrates. If shivering were stopped by curare or insulin the respiratory quotient was found to drop also. Though shivering will raise the metabolism, it is not the only factor involved for a rise in metabolism can be observed in animals that do not shiver (51). This rise is probably due to an increased muscle tone.

The secretion of epinephrine is found to increase on exposure to cold and is accompanied by an increase in blood sugar (10, 51). According to the work carried out on humans in Germany during World War II, hypothermia is associated with a blood sugar rise up to 180% of the original and was found to be a mirror image of the temperature curve. The blood level did not fall until rewarming (1).

Evidence that this increase in blood sugar is due to a discharge of epinephrine is found in the fact that the increase is absent when the splanchnic nerves are cut (10).

As stated before, shivering in dogs stops at 22° C. to 30° C. at which time the temperature regulating mechanism fails and metabolism decreases. At this level, however, the circulation and respiration can usually still be proven adequate.

On exposure to cold, respiration rises initially as does the metabolism. The human subjects in the German experiments (1) complained that they felt as though "an iron ring was drawn around their chests." Their breathing was observed to be inhibited and asthmatic in character. Guinea pigs in their early phases of hypothermia exhibited hyperpnea (23). Their maximal ventilation occurred at 35° C. and averaged 180% of the pre-immersion values. Below 33° C. the ventilation diminished progressively with the temperature. Relative to the oxygen uptake, the ventilation remained more than adequate to the stage of terminal apnea thus eliminating external respiration as the cause of the progressive fall in oxygen consumption.

In contrast to the above finding Grosse-Brockhoff and Schoedel (25) found in dogs the respiratory rate begins to decrease at 31.2° C. whereas the metabolism starts to decrease at 28.5° C. Swift (51) contends the rate of respiration begins to decrease while the metabolism is still increasing.

In rabbits the cyanosis which develops at 20° C. might be an indication of respiratory failure (2) but also may be circulatory failure. It is frequently noted that on autopsy the blood appears to be dark indicating respiratory failure or hypoxia (1, 2, 49). It was found that administering oxygen was of no help.

By observing some of the effects of hypothermia on circulation, respiration, and metabolism, it can be seen that the interdependence of these factors makes it difficult to designate any one of the three as the cause of death. The cause of death would appear to be an algebraic summation of these factors.

The variability of different species to withstand cold temperatures is demonstrated by a list of survival times given by Horvath et al. (33) of animals subjected to temperatures of -34° to -37° C. and surrounded by an air environment.

Animal	Survival Time in Hours
Mouse, Carworth CFI strain	0.4 hr.
Canary	0.6
Rat, Wistar	0.75 to 1.6
Albino	2.0
Rabbit, New	3.5 to 5.0
Zeland, white	5.0 to 16.0
Chicken, white	3.3 to 16.0
Leghorn	16.0 to 29.5
Pigeon, Army	22 to 24
Carrier	24 to 28
	48 to 78

Woodruff (49) in comparing survival of animals cites the following as the lowest body temperatures that non-hibernating mammals can withstand.

rabbit	20° C.
cats	16° C.
dogs	22.2 - 27.8° C.
monkeys	12.2° C.

According to the German work, (1) the human limit is 24.2 to 25.7°C.

It is interesting to note that though the species variabilities of survival in cold are great, their reactions to the cold are similar. For example, the cold-blooded animals, birds and mammals, show a decrease in all functions (45) with a drop in body temperature. The sequence of events leading to ultimate death in dogs and humans (1, 31) shows how interchangeable the reactions to cold in the two species are.

With the following data from experiments on dogs, an attempt will be made to show some effects of hypothermia on the circulation, metabolism and respiration. These changes are found to be paralleled in other animals.

METHODS

Experiments to determine the cardiac output and blood gas concentrations under hypothermic conditions were performed on a group of unselected but generally healthy mongrel dogs.

Induction of Hypothermia

The dogs, lightly anesthetized with a minimum dose of sodium pentothal intravenously, were secured in the supine position on an animal board. After the surgery necessary to insert equipment, the preparation was lowered into a tub of ice water of about 2-5° C. so that all but the head, neck, and ventral portion of the chest were immersed (41). In some of the experiments sodium pentothal was used to narcotize the animal initially followed by ether inhalation to maintain the level of narcosis.

Additional anesthetic was administered when indicated to keep the level of narcosis adequate (sodium pentothal or ether). Below 35° C. rectal temperature, the narcotic effect of the cold was usually sufficient to augment the anesthesia and keep the dog quiet. All animals were cooled to terminus (cardiac standstill).

To alleviate clotting, heparin was injected into the blood stream. Samples of arterial and venous blood were drawn for studies of blood oxygen and carbon dioxide concentration, cardiac output and pH.

Temperature

A continuous record of temperature changes was obtained by a thermocouple inserted 15-20 centimeters into the rectum, recording on a Leeds and Northrup Speedomax. It was necessary to manipulate the position of the thermocouple so that it could least easily be palpated through the abdominal wall. It was found that if the thermocouple were pointed toward the periphery fluctuations in the record occurred, presumably related to changes in position of the thermocouple with peristalsis.

Equipment for Blood Samples

A number 8 French catheter was inserted into the right ventricle by way of the external jugular vein. The catheter was inserted without the aid of a fluoroscope but moderate accuracy in this procedure was attained by previously curving the tip and measuring the distance from the incision to the heart.

It was possible, by means of auscultation or palpation, to determine that the catheter produced extra systoles upon entrance into the right atrium. When pulsations of the heart transmitted through the catheter could be seen at the syringe into which blood samples were drawn, the catheter was connected to a saline drip bottle to prevent clotting between samples. At the termination of each experiment the position of the catheter was verified by autopsy, for only when the catheter was placed in the right heart were the results valid.

To draw arterial samples, a through and through cannula was inserted into the carotid artery. These samples were drawn by means of a side arm

closed by a sterile bottle cap so that a syringe needle could be inserted and withdrawn many times without leakage.

Figure 1 illustrates the through and through cannula and the catheter inserted in the carotid artery and external jugular vein respectively.

Drawing Arterial and Venous Blood Samples

Venous blood samples were drawn from the catheter inserted into the right ventricle and arterial samples from the through and through cannula in the carotid artery. (Figure 2, drawing of arterial sample) Using a B and D three-way-stopcock, the catheter opening could be quickly changed from the saline drip bottle to a syringe. To draw a sample, it was necessary to first remove the saline from the catheter and then draw the blood into a second syringe. This maneuver necessitated the use of a second stopcock. The second syringe, in which the blood sample was stored in an ice bath until analyzed, was previously oiled and heparinized to prevent clotting and seepage along the barrel. The quantity of heparin used was minimal so that its volume in relation to dilution of the blood was negligible. One drop of lactic acid was added to about 10 cc. of the heparin solution to insure the retention of carbon dioxide in the blood. A drop of caprylic alcohol was also added to the heparin to prevent foaming and thus assure anerobic conditions in the syringe. After the samples were taken (at control, 35°, 30°, 25°, and when possible 20° rectal temperature) mercury was drawn into the neck of the syringe to serve as a seal and a small drop drawn in to facilitate mixing of the blood before analysis. The samples were then stored in ice water and all analyses performed within

Figure 1. A through and through carotid cannula and a catheter inserted in the right heart by the external jugular vein.

Figure 1. A through and through carotid cannula and a catheter inserted in the right heart by the external jugular vein.

Figure 2. Drawing an arterial blood sample from the carotid cannula.

four hours.

Oxygen Consumption

An endotracheal tube inserted in the dog was attached to a Sanborn respirometer. Continuous oxygen consumption records were obtained by rebreathing through soda lime.

Blood Pressure

Carotid blood pressures were measured with a mercury manometer attached to a #19 hypodermic needle inserted into the through and through cannula.

Femoral arterial pressures were measured (in some experiments) by using the same manometer but by cannulating the femoral artery.

Pulse

Pulse rate was obtained by palpation, auscultation, or by counting fluctuations in the mercury manometer.

Blood Gas Analysis

All blood gas analysis were performed by means of the Van Slyke and Niel manometric procedure for the combined analysis of carbon dioxide and oxygen.

Calculation of Cardiac Output

Using the data from simultaneous arterio-venous blood samples, and oxygen consumption, cardiac output by means of the Fick principle was

four hours.

Oxygen Consumption

An endotracheal tube inserted in the dog was attached to a Bunyon respirometer. Continuous oxygen consumption records were obtained by rebreathing through side line.

Blood Pressure

Carotid blood pressures were measured with a mercury manometer attached to a #19 hypodermic needle inserted into the thyroid and through cannula.

Femoral arterial pressures were measured (in some experiments) by using the same manometer but by cannulating the femoral artery.

Pulse

Pulse rate was obtained by palpation, auscultation, or by counting fluctuations in the mercury manometer.

Blood Gas Analysis

All blood gas analysis were performed by means of the Van Slyke and Neil manometric procedure for the combined analysis of carbon dioxide and oxygen.

Calculation of Cardiac Output

Using the data from simultaneous arterio-venous blood samples, and oxygen consumption, cardiac output by means of the Fick principle was

determined. Stroke volume was determined by dividing the cardiac output by the pulse taken simultaneously with the blood samples.

Respiratory Rate

Respiratory rate was measured directly from the oxygen consumption chart or visually when oxygen consumption was not measured.

Hematocrit

Hematocrit determinations were made on most blood samples.

pH

The pH of the whole blood was determined by means of a Beckman pH meter. Arterial samples used were drawn from the carotid cannula by piercing the sterile bottle cap with a #20 hypodermic needle. At frequent intervals the blood was drawn anerobically into a chamber surrounding a glass electrode (the two joining by a ground glass fit), and analyzed for pH within a few minutes. The blood sample was allowed to come to room temperature during the analysis. The justification for this procedure was that with the pH meter set at a constant (room) temperature the heat of the solution was found not to alter the pH.

RESULTS

Cardiac Output

Cardiac output was determined throughout the period of hypothermia in 15 dogs. At autopsy it was learned that the venous bloods were not withdrawn from the right heart in three of the series, therefore these animals were discarded from analysis. Three more of the dogs showed distinct signs of shock early in the cooling phase and so were likewise eliminated from the final analysis. The cardiac output data for the 12 dogs from which mixed venous blood was obtained (including those believed to be in shock, Nos. 31, 33 and 38) are presented in Table 1.

Of the 9 experiments used in the analysis the venous blood was obtained from the right ventricle in 8. In one it was obtained from the right atrium but, inasmuch as Cournand has shown that oxygen content of mixed atrial blood varies from mixed ventricular blood by less than 0.25 volumes per cent in dogs (12), these data are included in the analysis.

In Figure 3 is shown the average cardiac output expressed in liters per square meter body surface per minute. The computation of surface area in the dog is by the following formula from Dukes (18).

$$S = K \sqrt[3]{W^2}$$

Where

S = Surface area in M^2

K = A constant

W = Weight in kilograms

RESULTS

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Cardiac output was determined throughout the period of hypothermia in 15 dogs. At autopsy it was learned that the venous bloods were not withdrawn from the right heart in three of the series, therefore these animals were discarded from analysis. Three more of the dogs showed distinct signs of shock early in the cooling phase and so were likewise eliminated from the final analysis. The tabled output data for the 12 dogs from which mixed venous blood was obtained (including those believed to be in shock, Nos. 21, 23 and 24) are presented in Table 1.

Of the 9 experiments used in the analysis the venous blood was obtained from the right ventricle in 6. In one it was obtained from the right atrium but, inasmuch as Command has shown that oxygen content of mixed atrial blood varies from mixed ventricular blood by less than 0.2% volumes per cent in dogs (12), these data are included in the analysis.

In Figure 3 is shown the average cardiac output expressed in liters per square meter body surface per minute. The computation of surface area in the dog is by the following formula from Dubois (13).

$$S = K \sqrt[3]{W^2}$$

Where

S = Surface area in M^2

K = A constant

W = Weight in kilograms

Table 1. DATA FOR CARDIAC OUTPUT SERIES.

Dog No.	Body Area	39°C. Cardiac Index*	39°C. Pulse	39°C. O_2** Cons.	34°C. Cardiac Index*	34°C. Pulse	34°C. O_2** Cons.	29°C. Cardiac Index*	29°C. Pulse	29°C. O_2** Cons.	25°C. Cardiac Index*	25°C. Pulse	25°C. O_2** Cons.
26	.500	3.20	---	258.0	----	---	-----	1.20	90	72.0	0.60	20	32.0
27	.410	1.95	168	97.5	----	---	-----	1.46	--	63.4	1.46	41	26.8
29	.732	2.18	180	135.2	1.37	148	170.7	0.41	90	49.2	0.27	84	39.6
32	.732	3.96	182	155.8	4.51	---	495.9	2.73	128	269.1	0.82	116	39.6
34	.521	4.03	196	227.0	3.84	138	105.6	2.88	102	80.6	2.30	58	44.1
35	.716	4.89	172	244.2	3.91	114	100.6	5.17	90	136.9	2.05	46	32.1
36	.711	3.38	212	262.0	6.05	158	222.2	3.85	116	182.8	stopped breathing		
37	.448	2.34	140	143.0	1.02	140	162.9	1.56	105	102.7	0.89	26	26.8
39	.776	4.64	178	194.5	3.38	166	223.0	4.76	138	152.0	2.78	76	99.2
Avg.	.600	3.40	178.5	190.8	3.40	144	211.6	2.70	107.4	123.2	1.40	58.4	42.5
	+0.1	+1.2	+21	+60.3	+1.8	+18.2	+38.2	+1.5	+18.4	+52.2	+0.9	+32.2	+7.5
31	.462	5.41	152	138.5	2.16	124	64.9	Dog died					
33	.554	0.90	98	101.1	0.54	112	63.2	0.54	75	37.9	0.361	41	30.7
38	.516	1.40	170	137.7	0.40	178	67.8	0.28	128	36.8	0.101	79	15.5
Avg.	.500	2.60	140	125.8	1.00	138	65.3	0.40	101.5	37.4	0.200	60	23.1

* Cardiac index in L/sq. M/min.
** Oxygen consumption in cc/sq. M/min.

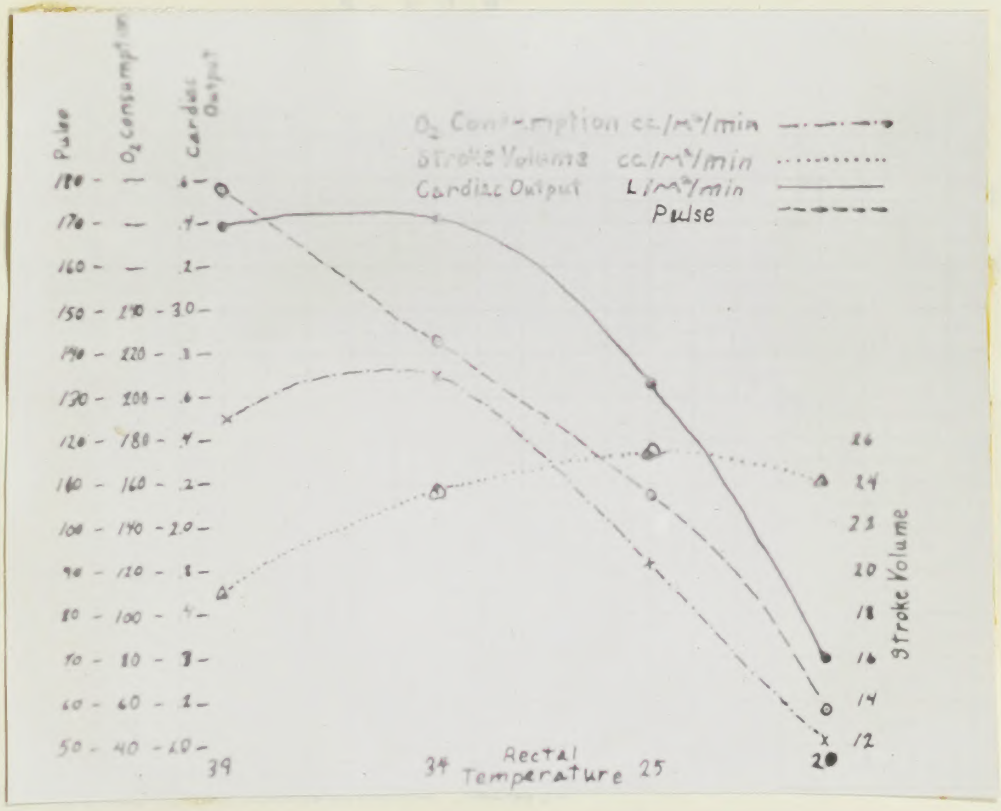

Figure 3. Graph of the average cardiac output, respiration, pulse, stroke volume plotted against temperature.

The constant in the above formula applicable to dogs has been given as 0.103 to 0.112. Arbitrarily the value 0.112 has been used as the constant in all calculations of this thesis, after Lusk (38).

To illustrate the methods by which the computations were carried out, the data from dog 37 have been applied to the formula as follows:

$$S = k\sqrt[3]{W^2}$$

$$S = 0.112\ \sqrt[3]{8^2}$$

$$S = 0.448 \text{ square meters}$$

Oxygen consumption in cubic centimeters per minute, S. T. P., can then be converted to cubic centimeters per square meter per minute.

$$\text{cc. } O_2/\text{min.} \div S = \text{cc. } O_2/M^2/\text{min.}$$

$$64 \div 0.448 = 143 \text{ cc. } O_2/M^2/\text{min.}$$

The calculation of cardiac output:

$$\text{cardiac output} = \frac{\text{oxygen consumption (cc./min.)}}{\text{arterial } O_2 \text{ content (cc./liter)} - \text{venous } O_2 \text{ content (cc./liter)}}$$

$$= \frac{64}{176 - 115} = 1.05 \text{ liters}$$

The cardiac output was then converted to the cardiac index (Cardiac output in liters/meter^2/min.):

$$\text{cardiac index} = \text{cardiac output} \div \text{surface area}$$

$$= 1.05 \div 0.448$$

$$= 2.34 \text{ liters}/M^2/\text{min.}$$

To determine the stroke volume in cc./meter^2/minute:

$$\text{stroke volume} = \text{cardiac index} \div \text{pulse rate}$$

$$= 2.34 \div 140$$

$$= 0.01673 \text{ liters}/M^2/\text{min.}$$

$$= 16.7 \text{ cc.}/M^2/\text{min.}$$

Stroke volume is more commonly computed in cc. of blood per stroke but in this case, since the cardiac index was employed, it was desirable to keep the same units of measurement.

Returning to figure 3 it can be seen that the cardiac output is maintained at almost a normal level to 34° (average) rectal temperature at which time it drops. One can also see from this graph that the oxygen consumption of these animals rises initially (possibly due to shivering) during the period at which the cardiac output remains elevated.

The two curves at 35° begin to drop steeply along with the temperature. At the same time the pulse can be seen to decrease linearly with the temperature and not reflect the early period of compensation. The stroke volume shows a steady increase to 29° C. and falls off slightly at 25° C. The autopsy findings that the heart of the hypothermic dog is usually greatly distended substantiates this observation.

Blood Gases

Simultaneously withdrawn arterial (carotid) and venous (right heart) blood samples were analyzed for their oxygen and carbon dioxide contents at various levels of reduced body temperatures. Two series of experiments were conducted, one breathing room air and the other breathing 100% oxygen. The results of these two studies will be presented in that order.

Following standardization of technique 10 dogs were observed in the first series. In one of these it was discovered at autopsy that venous bloods had been obtained from the superior vena cava (carrying a large percentage of cranial blood) rather than the right heart. The results obtained in this experiment differed sufficiently from those in which

mixed venous blood was drawn as to indicate a study of brain metabolism as opposed to that of the rest of the animal. It was not possible to conduct such an experiment before the preparation of this thesis, however, due to lack of fluoroscopic aid in placing catheters.

From the arterial and venous samples may be deduced the relative state of metabolism, circulation and respiration. The arteriovenous carbon dioxide and/or oxygen concentration difference, is a reflection of metabolism. The adequacy of the circulation for the prevailing metabolic demand can be determined by the relative percentage of venous carbon dioxide. If the concentration is decreased, the circulation is considered more than adequate for the metabolism. The arterial carbon dioxide as well as the arterial oxygen, may be considered indicative of the respiratory condition.

Examining the individual records in the manner described it is possible to determine the relative condition of the animal at various temperatures. In three of these nine dogs the respiration shows evidence of failure before 25° and is relatively good in the remaining six. By 20° two dogs have died, four have stopped breathing and the respiration of the remaining three is fair for the conditions, but failing.

Examining the circulation in a like manner, we can see that in all 9 animals the heart stopped beating at a lower temperature than cessation of respiration. The circulation is found to be adequate in all animals by 25° though in one case it appears to lag behind the metabolism at 30°. At 20°, the circulation in the 7 living dogs appears to be adequate. In 5 of these 7 it is definitely more than adequate as evidenced by the steeper increase in arterial carbon dioxide than the venous and the fact

that the venous oxygen concentration remains elevated as the arterial decreases (indicating respiratory failure). In addition, the hearts in these five animals continue to beat below 17° C. (16.8° to 11°C.).

The relative competence of circulation and respiration in the intact animal can be determined from these data. At 30° the circulation is better than the respiration in three dogs, equal to the respiration in two and inferior in four. From 25 degrees to terminus the circulation appears better than the respiration in all animals.

In figure 4 are plotted the average curves of the arteriovenous carbon dioxide and oxygen concentrations as well as the average hematocrit readings. An analysis of the averages of the series breathing air will reflect the overall trend seen in the individual dogs, but inasmuch as one extreme result in a small series can have undue influence of averages it is impossible to draw broad conclusions from these curves. But for what average curves represent it may be seen that the fall in the arterial and venous carbon dioxide concentrations indicate that both respiration and circulation are more than adequate for the metabolism to 30°. Between 30° and 20° the respiration begins to fail as evidenced by the increase in carbon dioxide and decrease in oxygen contents of the arterial blood. It still appears to be adequate for the metabolism however, as the venous components do not reflect much change from normal. By 20° the respiration is failing rapidly as can be seen by the sharp increase in the arterial carbon dioxide concentration and the lack of complete saturation of the arterial blood with oxygen.

The circulation as indicated by the venous oxygen and carbon dioxide, is seen to improve down to 25°. At 20° it is still quite good relative to

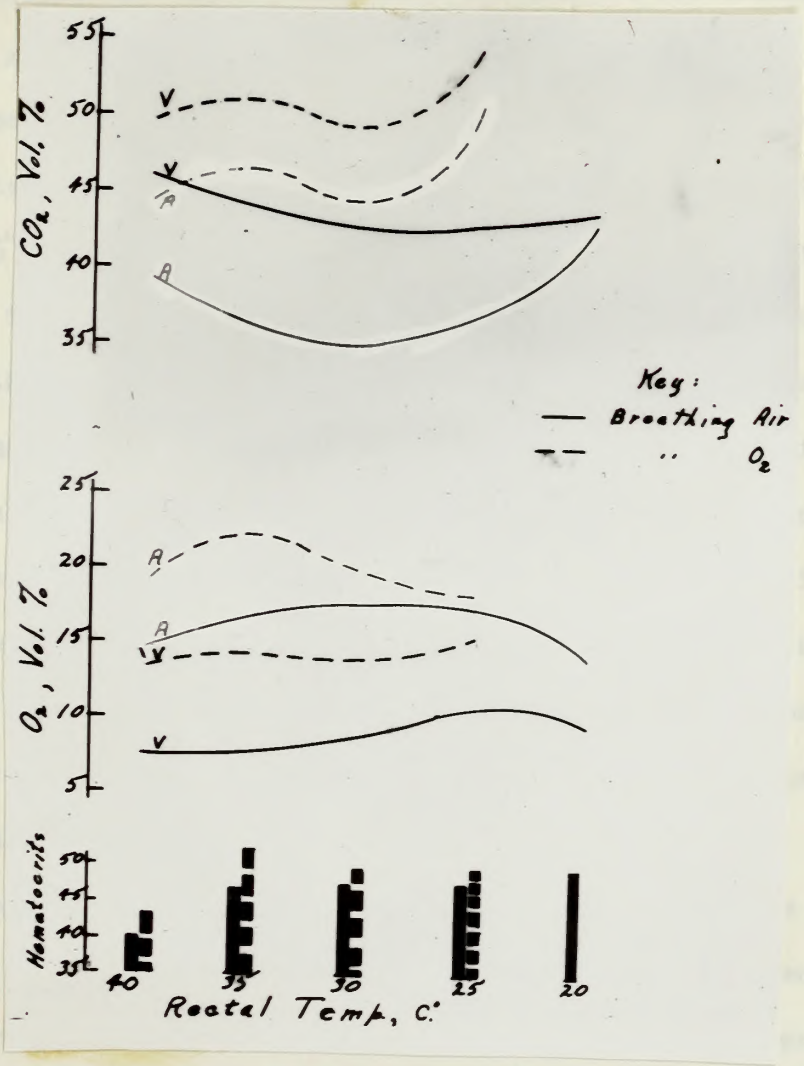

Figure 4. Graphs of average arterial and venous oxygen and carbon dioxide concentrations of groups breathing air and 100% oxygen.

the metabolic demands for in spite of the considerable changes in the arterial bloods the venous components are changed but little from normal.

In reviewing the data of the nine dogs breathing 100% oxygen, the respiration by 30° is found to be failing in five dogs, maintaining a level in two and is good in the remaining two. The respiration between 30° and 25° is still on the decline for it is failing in five, approximately normal in three and good in one. Between 25 - 20° one dog died and seven of the remaining eight stopped breathing. The respiration of the one dog was good to 25° but by 20° evidence of approaching failure is present, although it is still apparently adequate for the conditions.

The circulation in these dogs breathing 100% oxygen is failing in one of the nine above 25°. The eight survivors maintained adequate circulation to below 20°. Without exception, the respiration was seen to stop before any evidence of circulatory inadequacy was reflected in the blood metabolic gases.

Noting the average graphs of figure 4 for the series breathing 100% oxygen, it is seen that the respiration shows some impairment at 35°, but circulation remains good. Between 35° and 30° there is some improvement in respiration but by 25° approaching failure is apparent while the circulation remains adequate.

Comparing the two groups of dogs one can see that from control to terminus the respiration of those breathing oxygen shows progressive failure but is maintained quite well to 25° in those breathing air. A turning point after which failure of respiration and circulation become progressively more rapid, indicates the beginning of compensatory inadequacy. In the animals breathing oxygen this change occurs close to 30°

whereas in the group breathing air the turning point is closer to 25°. The group of dogs breathing 100% oxygen throughout the experiment exhibits a higher concentration of arterial and venous oxygen and carbon dioxide concentration, in vivo, at low temperatures.

An increased concentration of oxygen is explainable on the basis that the solubility of a gas is increased in a cold solution and that the water vapor pressure in the lungs, reduced by the cold, will enable a rise in the partial pressure of oxygen. Physiologically, the hemoconcentration, together with an increased affinity of hemoglobin for oxygen and a decreased cellular metabolism, will also be an important factor for the increase in the blood oxygen concentration.

In both groups of animals the hematocrits showed an initial rise probably due to the removal of the influence of sodium pentothal (42). After the initial rise, however, the level remains elevated indicating a hemoconcentration effect of the cold. In both series the rise due to cold (Figure 4) is in agreement with the 14 - 20% rise found by Bernhard (9).

pH

pH determinations were carried out on carotid blood of 10 dogs at regular intervals as they were being cooled. On figure 5 is plotted a graph of the theoretical pH shift necessary to raise the pO_2 in compensation for the shift due to cold.

Brown and Hill (11) and Dill and Forbes (17) have determined the shift to the left of the oxygen dissociation curve with reduced blood temperature. Using certain established physico-chemical properties of blood under these conditions the pH shift necessary to compensate for the

drop in temperature can be calculated. Using the curves from Brown and Hill (11) and Dill and Forbes (17) the pO_2 of blood at different temperatures with a constant pH can be determined. For these graphs the 50% level of saturation, which closely resembles the venous saturation, has been used as a reference point. From these curves the pO_2 at temperatures from 38° C. to 15° C. can be determined. These interpolated pO_2's, together with the change in pO_2 due to the reduced temperature, are listed in the following table:

Temperature °C.	pO_2	pO_2
38	28	0
35	25	3
30	19	9
25	15	13
20	11	17
15	9	19

The next step involves calculating the pH necessary to shift the dissociation curve back to the right to overcome the pO_2 to the left. Dill, Edwards, Florkin and Campbell (16) have determined the relationship between the dissociation curve of dogs blood and the pH of the blood cells (pH_c). Using this curve the pH_c necessary to compensate for the shift to the left can be computed. Since in the published curve of Dill, Edwards, Florkin and Campbell, the log pO_2 (at Hb O_2 = 50%) is plotted against the pH_c, the pO_2 must be converted to logs. Also, since the shift necessary at each temperature increases with decreasing temperature as shown above, the pO_2 for which the pH_c will be determined are 28 + 3, 28 + 9, 28 + 13, etc. for the respective temperatures. The results are as follows:

$\log$ (pO_2 28) $= 1.45 = pH_c$ 7.15

$\log$ ($p\,O_2$ 28 + 3) $= 1.49 = pH_c$ 7.08

$\log$ ($p\,O_2$ 28 + 9) $= 1.57 = pH_c$ 6.93

$\log$ ($p\,O_2$ 28 + 13) $= 1.61 = pH_c$ 6.86

$\log$ ($p\,O_2$ 28 + 17) $= 1.65 = pH_c$ 6.80

$\log$ ($p\,O_2$ 28 + 19) $= 1.67 = pH_c$ 6.76

For experimental comparison it is more useful to have the pH_c's converted to pH_s's (serum) since all pH determinations of whole blood will be essentially that of the serum (Parsons cited by Cullen (14).

Using the relationship established by Dill, Edwards and Consolazio (15) it is possible to convert pH_c to pH_s. This conversion was facilitated by the construction of a graph from their data using whole number pH_s's. This graph is pictured in figure 5.

The calculations were as follows pH_s 7.4 = $\log 3.981 \times 10^{-8}$.

Using Dill's graph (fig. 3) (15) find r, as the mean between the oxygenated and reduced r_H.

Then $3.981 \times 10^{-8} \div 0.61 = 6.526 \times 10^{-8}$

$- \log 6.526 \times 10^{-8} = 7.185 = pH_c$

Using the same method of calculation for the following whole number pH_s's:

pH_s 7.4 = pH_c 7.185 r = 0.61

pH_s 7.3 = pH_c 7.120 r = .66

pH_s 7.2 = pH_c 7.045 r = .70

pH_s 7.1 = pH_c 6.975 r = .75

pH_s 7.0 = pH_c 6.900 r = .795

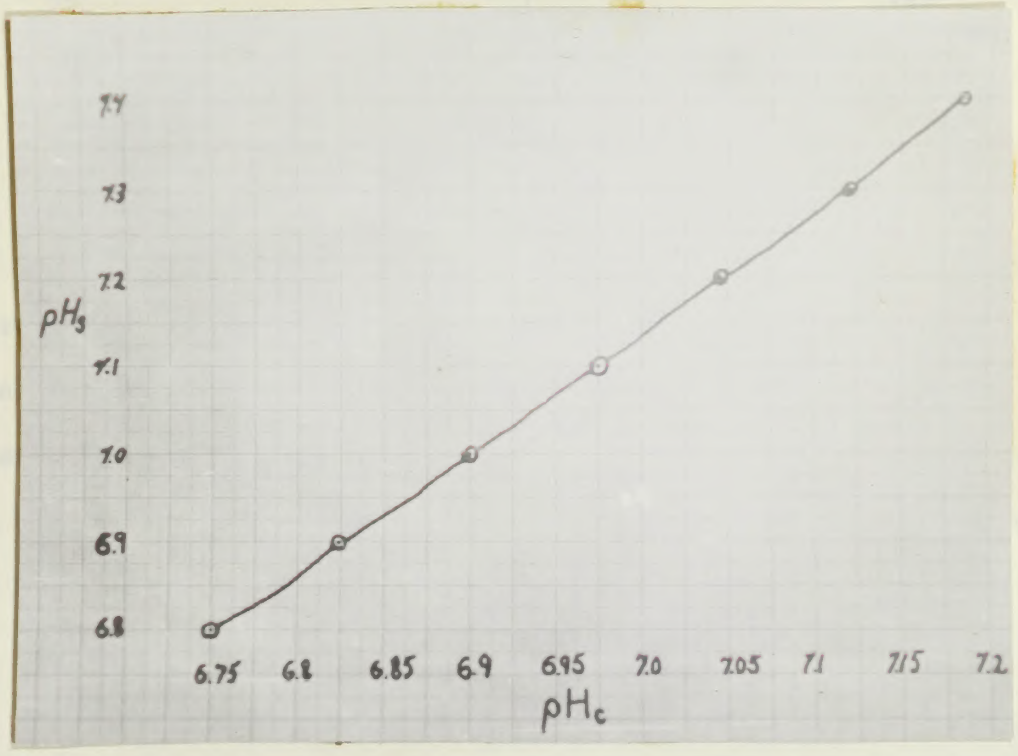

Figure 5. Graph relating pH_c to pH_s.

Figure 5. Graph relating pK_2 to pK_1.

pH_s 6.9 = pH_c 6.824 r = .84

pH_s 6.8 = pH_c 6.752 r= .895

From Fig. 5:

Temperature °C.	Shift to left of pO_2 with cold	pH_s to oppose shift to left
38°	--	----
35°	3	7.25
30°	9	7.04
25°	13	6.95
20°	17	6.87
15°	19	6.80

These pH_s are plotted on figure 6 as the theoretical curve.

The mean and standard deviations from the mean are plotted on Figure 6 against the rectal temperature. One can see that as the rectal temperature is reduced the pH also decreases. In the lower temperature range, below 24° the two curves approximate and indicate that the dogs might be better adjusted to their environment than they were between 30 and 24° C.

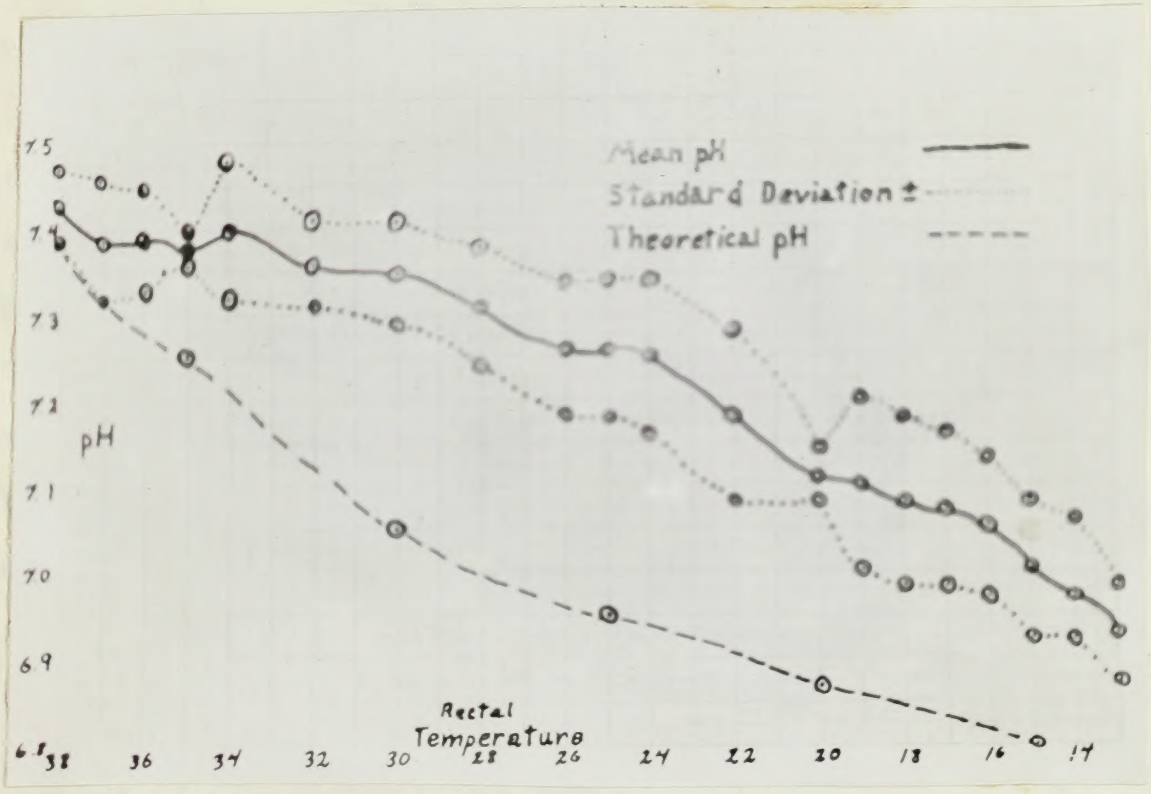

Figure 6. Mean pH of blood and standard deviations plotted against temperature.

Figure 6. Mean pH of blood and standard deviations plotted against temperature.

DISCUSSION

As seen from the results of two series of dogs subjected to hypothermia, one breathing 100% oxygen and the other air, the group breathing oxygen suffers respiratory failure at the higher temperature. This agrees with Woodruff (54) who found that oxygen administration to dogs subjected to hypothermia was not beneficial and might even be detrimental.

In comparing the two series still further it can be seen that they show a similar pattern. Figure 4, picturing the average arterial and venous carbon dioxide and oxygen contents respectively, shows that the blood gases of the dogs breathing oxygen are higher than those on air. This high concentration of oxygen in the group that can least adjust makes the theories proposed by von Werz (53) and elaborated by Rein (cited by Alexander (1), that hypoxia is the cause of death unlikely, since the blood is capable of releasing considerable oxygen as evidenced by the decrease found in the oxygen concentration in the dogs at 20° C. as compared with the high concentration before immersion. It must be remembered that the oxygen and carbon dioxide concentrations as determined by the Van Slyke method include both physically dissolved and chemically combined gas. By action of the decreased temperature, the oxygen dissociation curve shifts so that oxygen will not be as easily released. At the same time, the physically dissolved oxygen increases to a level that may well be adequate for the existing reduced metabolism, especially in those dogs breathing 100% oxygen.

The contention that hypoxia is a foremost contributing factor to death is well established. It has been stated that below a certain temperature the blood returns as arterial blood after circulating through chilled tissues; that in cold, the hemoglobin will not relaese its oxygen to the tissues (1). From this lack of oxygen local suffocation is believed to take place. By electroencephalographic studies, however, it was found that anoxic patterns were not formed by the brain of a cold animal (1). The observation that venous blood is almost black at autopsy whereas the blood in the left heart was red, is an indication that the blood is capable of releasing its oxygen. Though it has been found by some that the pH change in the blood is slight or negligible (53) the experimental results of this laboratory indicate a pronounced decrease along with temperature.

Our findings of a cardiac output and oxygen consumption decrease from 34° to terminus, an essentially linear pulse rate decline from 39°, and the increased stroke volume in the 29° - 25° range followed by a decline is in agreement with Crismon's (12) compensatory adjustment and progressive circulatory failure in rats. When the dog is cooled past the compensatory period, however, the decrement in cardiac output is not due to a decrease in stroke volume as believed by Crismon, but is related to the reduced pulse rate. These same general characteristics have been found in humans by Kossman (35).

Aside from a decreased pulse rate reducing the cardiac output there are other factors to which this action can be ascribed. A general shift of the body fluids from the blood stream to the peripheral tissues (4) reduces the volume of the circulating blood, as well as increasing its

viscosity and specific gravity (54); thus increasing the load on the heart. A peripheral vasoconstriction will tend to equalize the fluid shift by confining the majority of the blood to the viscera. The increased stroke volume may be stimulated by this added load. When the temperature regulating mechanism is overcome it appears as though all mechanisms become depressed including the cardiac output.

A series of experiments has been carried out by Shriber (46) to study the mechanisms of the hypothermic heart. According to Shriber, the duration of systole, isometric contraction and isometric relaxation are all prolonged. This he defines as the period of cardiac activity since during these actions the cardiac muscle is exhibiting tension.

In the cold animal all these phases are prolonged, so the activity period is lengthened with respect to the cardiac cycle. With the heart in vivo at a temperature of 22° C. the activity cycle is prolonged so when the pulse rate is 50 per minute, the period of activity occupies 68% of the time. Under normothermic conditions the activity cycle of a heart beating 50 times a minute, occupies 35% of the time.

From these time relations it can be seen that more time is spent in activity by the cold heart than the warm heart at comparable rates. Conceivably then, since all components of the active portions of the cardiac cycle are probably affected equally by the cold, and the activity phase occupies a longer period, the heart may go into metabolic debt from which it fails to recover.

These factors might be more clearly illustrated by analyzing the blood gas record of an animal in which the typical compensatory mechanisms can be picked out (Figure 7).

By the sizeable arteriovenous difference in the pre-immersion (39° C.) and 30° C. samples a high metabolic rate is indicated. The high metabolism can be explained by progressive shivering from 38° to 30° where it is seen to be intense, as noted in the protocol. Shivering decreases from 30° to 25° and is reflected by the decreased metabolism. With a lower metabolism the circulation and respiration could well be expected to be more than adequate.

By the decrease in the venous carbon dioxide between the 39° and 30° samples it is evident that the circulation is adequate for the metabolism. Between 30 and 25°, as the shivering decreases, the relative competence of the circulation increases, as evidenced by the steep drop in venous carbon dioxide and continued rise in oxygen. That the circulation remains more than adequate until serious respiratory failure is indicated by the constant rise in venous oxygen and the maintenance of venous carbon dioxide at a lower than control level. The respiratory condition during the period of shivering increase is seen to be inadequate as indicated by the arterial gas content. On the other hand it is more than adequate as the metabolic demands subside as evidenced by the drop in carbon dioxide concentration and increase in oxygen content. The latter is aided by the concurrent hematocrit rise. The respiration, though competent in this period of adjustment, is seen to lag slightly behind the circulation since the venous carbon dioxide fall is faster than that of the arterial. Between 25 and 20° C. a rise in arterial carbon dioxide and a decrease in oxygen indicate the beginning of respiratory failure even though its condition is sufficient for the metabolic demands of this temperature. Past 20° the failure is critical. The metabolic demands of

the heart referred to by Shriber (46) are probably not met due to respiratory failure, so the circulatory failure follows closely.

From the protocol respiratory cessation was noted to occur at 17.7° and cardiac arrest at 16.4° C., just prior to the last sample of bloods. With the last sample the interesting phenomenon of the arterial carbon dioxide content exceeding that of the venous was observed. This anomalous condition, observed in two other dogs, can only be explained by capillary blood drawn back from the brain into the arterial sample since the withdrawals were made at cardiac standstill.

As noted before, the oxygen content follows the hemoconcentration due to the combined effect of the recovery from pentothal sodium (42) and the water shift due to cold (2, 44, 50).

The RQ of non-shivering hypothermic animals has been found by some investigators to decrease (21, 51). On this evidence the theory that the metabolism was changed to utilization of the fats and proteins rather than carbohydrates was established. The RQ drop is partially due to metabolic change, but may also be a product of the increased physical solubility of carbon dioxide in the cold blood (17). Nevertheless, the incomplete cellular metabolism found under hypothermic conditions, whether due to a change in metabolism or chemical activity reduced by cold, will probably increase the production of keto-acids lowering the pH of the blood (53).

The decreased pH as was shown before, will increase the pO_2 thus decreasing the possibility of hypoxia. The pH of the hemoglobin in the blood cells is still lower than that of the serum, thus further facilitating the release of oxygen from the blood to the tissues in the

hypothermic animal.

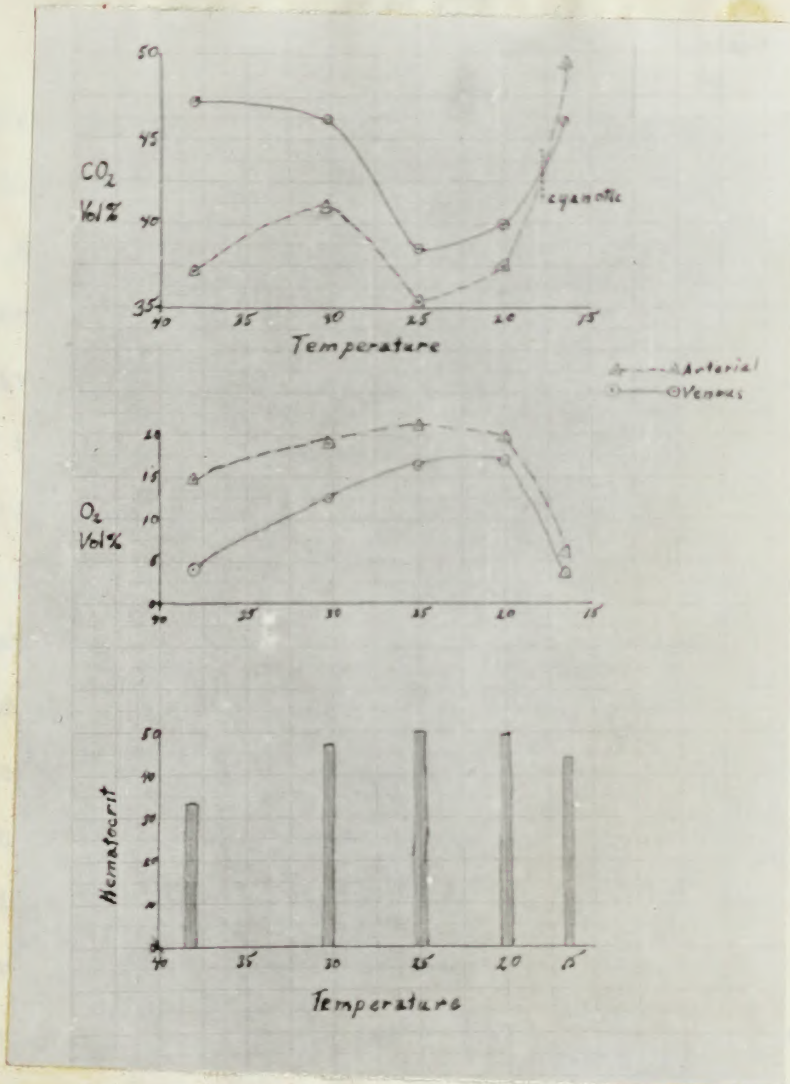

Figure 7. Graph of blood gas concentrations of dog breathing air.

CONCLUSION

Data from experiments performed on two series of dogs, one breathing air, the other 100% oxygen, subjected to immersion hypothermia under pentothal sodium anesthesia have indicated that respiration generally failed before circulation. A study of blood gases was made to evaluate the relative adequacies of respiration, circulation and metabolism. It was found that the respiration of the animals that breathe 100% oxygen evidenced failure at a higher body temperature than those of the series breathing air. Circulation in both series was found to be sufficient for the metabolic demands almost to terminus.

Observations concerning cardiac output, pulse, oxygen consumption and stroke volume were made. It was found that the cardiac output reflected the oxygen consumption which, in turn, was related to the degree of shivering. Both showed a slight initial rise before beginning the progressive decrease at 34°. The pulse, on the other hand showed a linear decriment with the temperature but the stroke volume rose until 29°, then began to decrease.

A study of the hydrogen ion concentration with respect to its influence on the oxygen tension was made. Findings from this series of experiments indicated that the pH of the blood decreased progressively as the body temperature was lowered.

It is well known that a decrease in pH will affect the oxygen binding capacity of the blood opposite to that of cold. A theoretical analysis was made to determine the pH change necessary to restore the

oxygen tension to the normothermic level when the animal was in various stages of hypothermia. This evidence may be taken as refutation of the theory that the blood per se of a hypothermic animal could not release its oxygen to the tissues with the result that hypoxic hypoxia ensued. Evidence other than pH studies that would show this theory in error was that of the dogs breathing 100% oxygen experienced respiratory failure before those that breathed air.

Data from one dog, in which the catheter was placed in the superior vena cava, suggested that a series of experiments be performed to analyze the blood from the brain and compare it with blood from other parts of the body. This study would show whether the hypothermic brain metabolism differs materially from that of other organs of the body.

More information on these topics would throw light on the mechanism responsible for the ultimate death seen in hypothermia. From the present evidence the failure seems to be due to a depression of nervous and metabolic function by cold per se and the lack of accumulating sufficient stimulation necessary to fire centers, such as the respiratory center, to maintain life.

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ABSTRACT

With data from three series of dogs subjected to immersion hypothermia, observations were made regarding cardiac output, blood gas content and blood pH.

All animals were anesthetized with pentothal sodium and maintained by pentothal sodium or ether. Surgery was performed for insertion of the necessary equipment to draw blood samples. The mixed venous blood was obtained from an indwelling catheter inserted into the right heart by way of the external jugular vein and the superior vena cava. Arterial blood samples were obtained in all three series from the side-arm of a through and through carotid cannula.

To determine cardiac output changes, observations were made before immersion, at 35, 30, 25 and where spontaneous breathing was maintained, at 20 degrees rectal temperature. Samples of the arterial and venous blood taken at these intervals were analyzed for oxygen content by the Van Slyke manometric procedure and with the aid of a continuous record of oxygen consumption, cardiac output by the Fick method was computed. It was found that the cardiac output reflected the oxygen consumption which in turn was related to the degree of shivering. Both showed a slight initial rise before beginning a progressive decrease at 34 degrees. The pulse, on the other hand, showed a linear decrement paralleling the temperature but the stroke volume rose until 29 degrees, then began to decrease. The increase in stroke volume was verified by autopsy when it was seen that the right heart was greatly distended.

The increased stroke volume together with a decrease in cardiac output would indicate that an added strain is perhaps applied to the heart musculature and may represent a contributing factor to the ultimate cardiac failure in the terminal hypothermia.

Blood gas studies were performed on two series of dogs, one breathing air and the other 100% oxygen. By analysis of the oxygen and carbon dioxide content, the relative adequacy of respiration, circulation and metabolism was determined. The condition of these three factors was indicated by the carbon dioxide and oxygen concentration in the arterial and venous blood. The venous carbon dioxide concentration was considered as indicative of the circulatory and the arterial of the respiratory status. The difference in the two concentrations was considered a measure of the metabolism and the relative adequacy of the circulation and respiration was determined by the slopes of their graphs. If the venous carbon dioxide concentration decreased the circulation was considered more than adequate for the metabolic demands. When the venous concentration increased this was considered as evidence of circulatory failure. The respiratory condition was analyzed in a like manner.

The arterial and venous oxygen concentrations were also regarded in the same way. The arterial oxygen, an indication of the respiratory and the venous oxygen of the circulatory sufficiency. In these analyses, however, the hematocrit results were also taken into consideration. The results of the blood gas analysis showed that in the hypothermic dog respiration failed before the circulation. Comparing the two series of dogs, one breathing air and the other 100% oxygen, it was found that respiratory failure was evedenced at a higher temperature in the series

breathing oxygen. In both groups of experiments, however, the circulation remained adequate for the metabolic demands almost to terminus.

Findings from the group of dogs upon which blood pH was determined, indicated that the hydrogen ion concentration increased progressively as the body temperature was lowered. It is well known that a decrease in pH will affect the oxygen binding capacity of the blood opposite to that of cold. A theoretical analysis was made to derive the pH change necessary to restore the oxygen tension to the normothermic level when the animal was in various stages of hypothermia. This evidence may be taken as a refutation of the theory that the blood per se of a hypothermic animal could not release its oxygen to the tissues. Evidence other than the pH studies to show that the blood was capable of transporting oxygen is that the series breathing 100% oxygen experienced respiratory failure before those that breathed air. At termination of all experiments the oxygen content of the blood was decreased showing that the blood could release its oxygen.

Data from one dog, in which the catheter was placed in the superior vena cava, suggested that a series of experiments be performed to analyze the blood from the brain and compare it with blood from other parts of the body. This study would show whether the hypothermic brain metabolism differs materially from that of other organs of the body.

General conclusions drawn from these results indicate that the administration of oxygen under hypothermic conditions is detrimental. Ultimate failure due to hypothermia is not due to any one factor namely increased oxygen retention of the blood. The failure may be caused by a number of factors such as a reduction in metabolism and nerve conduction,

decreasing the stimulation to centers such as the respiratory and cardiac centers. It might therefore be postulated that the cessation of life in terminal hypothermia is due to an algebraic summation of the reduced sensitivity of the centers mentioned.

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